

DISCUSSION

Rejection of Claims 1-39 under 35 U.S.C. §112, First Paragraph

In the Office Action mailed September 10, 2002, the Examiner rejected claims 1-39 under 35 U.S.C. 112, first paragraph, as not being reasonably enabling for additional types of  $\alpha$ -adrenoceptor antagonists and muscarinic antagonists. The essence of the rejection is that, while the description is enabling for certain  $\alpha$ -adrenoceptor antagonists and certain muscarinic antagonists, no enablement is provided for other claimed  $\alpha$ -adrenoceptor and muscarinic antagonists.

It is well-settled that an inventor need not disclose every species of the invention. Rather, the claims "must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art." In re Fisher, 427 F.2d 833, 839, 166 U.S.P.Q. 18 (CCPA 1970). The fact that some experimentation is necessary does not preclude enablement; what is required is that the amount of experimentation must not be unduly extensive. "[A] considerable amount of experimentation is permissible. . . if the specification. . . provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice. . . the invention claimed." PPG Indus. v Guardian Indus. Corp., 75 F.3d 1558, 37 U.S.P.Q. 2d 1618, 1623 (Fed. Cir. 1996) (citing Atlas Powder Co. v. E. I. Dupont de Nemours & Co., 750 F.2d 1569, 1576, 224 U.S.P.Q. 409, 413 (Fed. Cir. 1984)).

The instant specification is fully enabling for additional  $\alpha$ -adrenoceptor antagonists and muscarinic antagonists because the ability to determine whether a compound is either an  $\alpha$ -adrenoceptor antagonist or a

muscarinic antagonist, the ability to incorporate combinations of such antagonists into pharmaceutical formulations, and the ability to evaluate the efficacy of such combinations, are all well within the purview of one of ordinary skill in the art, given the benefit of the instant disclosure. The  $\alpha$ -adrenoceptor antagonism of a compound may be determined using a number of well-known, conventional assays, including, for example, those disclosed in U.S. Pat. Nos. 5,599,810 and 5,340,814. The Examiner's attention is directed to page 5, lines 32-35, bridging to page 6, lines 5-6, of the instant specification. Similarly, the muscarinic antagonistic activity of a compound can also be easily determined using conventional methods including, for example, those disclosed in Wallis and Napier, *Life Sci.*, 64, 395-401 (1997). The Examiner's attention is directed to page 6, lines 23-25, of the instant specification. Similarly, the ability to prepare pharmaceutical formulations, including the presently claimed combinations will also be well known to the skilled artisan, given the benefit of the instant disclosure. The Examiner's attention is directed to the disclosure in Examples 1 to 5, set forth on pages 12 to 15. Finally, the efficacy of such combinations in treating symptoms associated with benign prostatic hyperplasia (BPH) may be determined according to the protocols set forth on page 15, lines 20- 36, bridging to page 16, lines 5-8 of the present specification.

The instant specification provides reasonable guidance in the selection of additional  $\alpha$ -adrenoceptor antagonists and muscarinic antagonists for use in the claimed compositions and methods, how to incorporate such combinations into pharmaceutical formulations, and how to determine the efficacy of such formulations in the claimed methods. Reconsideration

and withdrawal of the rejection of claims 1-39 under 35 U.S.C. §112, first paragraph, is requested.

Rejection of Claims 1-39 under 35 U.S.C. §102(b)

In the Office Action mailed September 10, 2002, the Examiner rejected claims 1-39 under 35 U.S.C. 102(b) as being anticipated by Heible, et al., and Ukimura. The basis of the rejection is that Heible, et al. and Ukimura both teach pharmaceutical compositions and methods of treating urinary tract ailments which comprise the use of combinations of α-adrenoceptor antagonists and muscarinic antagonists.

"Anticipation requires the presence in a single prior art reference disclosure of each and every element of the claimed invention arranged as in the claim." Lindemann Maschinenfabrik GmbH v. American Hoist & Derrick Co., 730 F.2d 1452, 221 U.S.P.Q. 485 (Fed. Cir. 1984) (citing Connell v. Sears, Roebuck & Co., 722 F.2d 1542, 220 U.S.P.Q. 193 (1983))

Claims 1-39 are not anticipated by either Heible, et al., or Ukimura because neither reference teaches or discloses pharmaceutical compositions comprising combinations of α-adrenoceptor antagonists and muscarinic antagonists, nor methods of using such combinations.

The Examiner alleges that Heible, et al. teaches compositions and methods of treating urinary tract ailments using both α-adrenoceptor antagonists (erroneously citing pages 285s - 286s) and muscarinic antagonists (citing pages 286s - 288s). Heible, et al., on pages 287s and 288s teaches the use of muscarinic antagonists in treating urinary incontinence, however, the citation to pages 285s and 286s, in the section entitled "3.2.1 ADRENERGIC STIMULANTS", in fact, teaches the activation of α-adrenoceptors, i.e., the use of α-adrenoceptor agonists, in treating urinary incontinence, and

not the use of  $\alpha$ -adrenoceptor antagonists. The Examiner's attention is directed to the text on page 286s, second full paragraph. The only teaching of Heible, et al. that mentions  $\alpha$ -adrenoceptor antagonists in a mutually inclusive context with another agent is set forth on page 283s in the section entitled "2.2.3 COMBINED THERAPY" where the combined use of  $\alpha$ -adrenoceptor antagonists and 5- $\alpha$ -reductase inhibitors is disclosed.

The Examiner has further alleged that Ukimura also teaches compositions and methods of treating urinary tract ailments using both  $\alpha$ -adrenoceptor antagonists and muscarinic antagonists. A plain reading of the first sentence of the abstract clearly indicates that the enumerated drugs were administered separately in a comparative study, one compound against the other, in an effort to determine the relative effects of each type of compound on the endpoints of bladder contractions, changes in micturition function, and urinary filling and storage phases. No combination therapy of any kind was expressly or implicitly employed.

In conclusion, nothing in either Heible, et al., or Ukimura teaches or discloses pharmaceutical compositions comprising combinations of  $\alpha$ -adrenoceptor antagonists and muscarinic antagonists, or methods of using such combinations. Reconsideration and withdrawal of the rejection of claims 1-39 under 35 U.S.C. §102(b) is requested.

Rejection of Claims 1-9 under 35 U.S.C. §103(a)

In the Office Action mailed September 10, 2002, the Examiner rejected claims 1-39 under 35 U.S.C. 103(a) as being unpatentable over Heible, et al, and over Ukimura in view of Heible, et al. The allegation is that one of ordinary skill in

the art would be motivated to employ combinations of  $\alpha$ -adrenoceptor antagonists and muscarinic antagonists, or compositions comprising such combinations, in treating urinary tract ailments related to BPH because:

(1) Heible, et al. teaches treatment of BPH and urinary incontinence with various compounds, including  $\alpha$ -adrenoceptor antagonists (citing pages 277s - 283s and 284s - 286s) and muscarinic receptor antagonists (citing pages 287s - 288s);

(2) Heible, et al. further teaches compositions and methods of treating urinary incontinence which comprise  $\alpha$ -adrenoceptor antagonists (erroneously citing pages 285s - 286s) and muscarinic receptor antagonists (citing pages 286s - 288s); and

(3) Heible, et al. also teaches that a form of incontinence can be induced by urethral obstruction, and therefore may be seen in patients with BPH.

With respect to allegations (1) and (3), Heible, et al. does teach, inter alia, treatment of BPH with  $\alpha$ -adrenoceptor antagonists (page 283s) and urinary incontinence with muscarinic antagonists (page 287s). However, these two classes of agents are never discussed in any mutually inclusive context. The only combination therapy of any kind taught in Heible, et al. is the combination of  $\alpha$ -adrenoceptor antagonists and 5- $\alpha$ -reductase inhibitors. Furthermore, urinary incontinence and BPH are etiologically distinct conditions. BPH is not a bladder disorder, but a condition of the prostate that induces urethral resistance, resulting in bladder outlet obstruction. Heible, et al. teaches that muscarinic antagonists are employed in treating urge incontinence, but

cautions that contractions of the bladder are inhibited thereby, resulting in urinary retention. Accordingly, Heible, et al. teaches away from the presently claimed combinations because one skilled in the art would understand that the use of muscarinic antagonists in treating symptoms associated with BPH would exacerbate the symptoms already attributable thereto.

With respect to allegation (2), Heible, et al. clearly does not teach compositions and methods of treating urinary incontinence which comprise  $\alpha$ -adrenoceptor antagonists (erroneously citing pages 285s - 286s) and muscarinic receptor antagonists (citing pages 286s - 288s). Heible, et al., on pages 285s and 286s, in the section entitled "3.2.1 ADRENERGIC STIMULANTS", teaches the use of  $\alpha$ -adrenoceptor agonists, in treating urinary incontinence, not the use of  $\alpha$ -adrenoceptor antagonists. The Examiner's attention is directed to the previous section of the instant Reply.

The relevance of the teachings of Ukimura with respect to the instant combinations has been addressed fully in the previous section of the instant Reply. To reiterate, nothing whatsoever in Ukimura teaches, discloses, or suggests the use of any combination therapy. The enumerated drugs were administered separately in a comparative study so as to determine the relative effects of each type of compound on the designated endpoints. The fact that Ukimura teaches the use of, inter alia, either  $\alpha$ -adrenoceptor antagonists or muscarinic receptor antagonists alone in treating spontaneous bladder contractions would not motivate one skilled in the art to employ a combination of both, as the use of such a combination would exacerbate the symptoms associated with BPH by inhibiting contractions of the bladder.

Neither Ukimura nor Heible, et al., either alone or in any proper combination, teaches, discloses, or suggests the desirability of pharmaceutical compositions comprising combinations of  $\alpha$ -adrenoceptor antagonists and muscarinic antagonists, or methods of using such combinations. Reconsideration and withdrawal of the rejection of claims 1-39 under 35 U.S.C. §103(a) is requested.

All claims in the application are in condition for allowance. Such prompt and favorable treatment is respectfully solicited.

Respectfully submitted,

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